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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/893,666	06/29/2001	Ichiro Yamashita	210217US0	9403

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/893,666	Yamashita, I.
Examiner	**Art Unit**
Joseph Woitach	1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Nov 1, 2002*.

2a) [ ] This action is **FINAL**. 2b) [X] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-17* is/are pending in the application.

4a) Of the above, claim(s) *1-5* is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *6-17* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [X] The drawing(s) filed on *Jun 29, 2001* is/are a) [ ] accepted or b) [X] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [X] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [X] All b) [ ] Some* c) [ ] None of:

1. [X] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [X] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [X] Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6
4) [ ] Interview Summary (PTO-413) Paper No(s).
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

DETAILED ACTION

This application filed June 29, 2001, claims benefit to foreign application No: 2000-247729, filed August 17, 2000 in Japan.

Claims 1-17 are pending.

Election/Restriction

Applicant's election with traverse of Group III, claims 6-17, in Paper No. 13 is acknowledged. The traversal is on the ground(s) that the Office has failed to meet the burden necessary to sustain a restriction requirement, citing MPEP 806.04 and 808.01. Further, Applicants argue that the Office has not shown that a burden exists in searching and thus should keep the claims together, citing MPEP 803. See Applicants amendment, page 2. This is not found persuasive because for a proper restriction **one** of two standards must be met: 1) the inventions must be independent or distinct, and 2) there must be a serious burden on the examiner if restriction is not required of a proper restriction has been met (emphasis added, MPEP 806.04 and 808.02). Further, MPEP 808.02 states that 'the Examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation of **one** of the following: (A) Separate classification, (B) separate status in the art when classifiable together, or (C) a different field of search' (emphasis added). In this case, Applicant does not contest that the inventions are not distinct, only that they are related and argue that one can be

used to create the other. In making the restriction requirement, Examiner has demonstrated each A and C as noted above. Each of the restriction groups represent different products as exemplified by their different classification, each requiring a separate search by both classification and text searches. Examiner would agree that the polynucleotide of group I could be used to generate a protein, however other conventional means to synthesize a protein exist in the art which do not require a polynucleotide. Further, while the polynucleotide of group I can be used to make the protein of group II, the two groups are not equal in that many other polynucleotide sequences besides SEQ ID NO: 1 could be used to generate the protein set forth in SEQ ID NO: 2, thus not requiring the polynucleotide of group I. Additionally, the restriction requirement has provided adequate reasoning of how the products are capable of separate use which are conventional in the art for polynucleotides, proteins and transgenic animals, noting specific and different uses for each the polynucleotide, protein and transgenic fish encompassed by each of the restriction groups. Applicants arguments are unpersuasive because Applicants have not provided any specific arguments to why the conclusions for the conventional use of each these products is incorrect, therefore, is maintained that the Office has met its burden for requiring a restriction requirement for the three different products. Further, Applicants argument that it would not constitute an undue search burden is unpersuasive because each of the products have separate classifications and no specific arguments have been presented to why search of each of the separate products would not constitute a search burden.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-17 are pending. Claims 1-5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. Claims 6-17 as they are drawn to a transgenic medaka fish and use thereof are currently under examination.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Accordingly, the instant application has been given the priority date of its filing, June 29, 2001.

Claim Objections

Claims 6 and 7 are objected to because of the following informalities: Claims 6 and 7 encompass the use of the products according to claims 1 and 2, which have been withdrawn as being drawn to a non-elected invention. Claims 6 and 7 should be amended to recite the specific embodiments of claims 1 and 2 to which they are accorded. For the sake of compact prosecution,

claims 6 and 7 will be interpreted to encompass the polynucleotide sequences set forth in claims 1 and 2.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic medaka fish comprising within its genome a polynucleotide encoding a medaka estrogen receptor as set forth in SEQ ID NO: 2 operatively linked to the medaka beta-actin promoter, wherein said transgenic medaka fish produces increased level of the estrogen receptor as compared to normal wild type medaka fish and produce observable thrombi when cultured in the presence of estrogen, and methods of use of said transgenic medaka fish in methods to detect estrogen in a sample and to develop transgenic medaka fish with thrombi, does not reasonably provide enablement for medaka fish which do not express the estrogen receptor, for other promoters besides the beta-actin promoter, or for the use of transgenic medaka fish which do not develop thrombi. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). This is particularly true in the art of transgenic animals with respect to transgene behavior. In general, transgene expression in different species of transgenic non-human animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding

human growth hormone (pages 276-277). The observation is further supported by Mullins *et al.* who report on transgenesis in the rat and larger mammals. Mullins *et al.* state that "a given construct may react very differently from one species to another" (page S39, Summary). Among different species of fish, Houdebine *et al.* teach that while external fertilization is a natural process and fish embryos can be easily obtained, there are may variations among species development which make the use various species eggs difficult in transgenics (page 891, bottom of second column). Further, the fate of the DNA injected into the egg, number of copies produced/integrated into the genome, and the resulting expression pattern was highly dependent on the transgene construct and the species of fish (summarized in abstract).

In the instant case, the specification teaches that use of the medaka beta-actin promoter provided an expression level of the estrogen receptor as set forth in seq id no: 2 which resulted in a hypersensitivity to the presence of estrogen. Takage *et al.* (IDS ref AW) teach that the beta actin promoter is a strong promoter capable of providing expression in a wide range of tissues tested (bridging pages 194-195), though initially the expression pattern varied from embryo to embryo (page 193, second column) and demonstrated positional silencing in all but one of the transgenic lines developed (page 196, figure 6). Thus, like other transgenic animals, medaka fish demonstrate the same variability in transgene expression as evidenced by the experiments with the beta actin promoter. Further, the ability of a estrogen receptor to elicit a specific affect will be a consequence of the specific estrogen receptor expressed , the specific tissues in which it is expressed, the specific levels at which it is expressed and the complexity of the pathway in which

it participates. For example, Kawahara *et al.* teach the characterization of a related medaka estrogen receptor. Kawahara *et al.* teach that in normal medaka fish, the consequence of estrogen treatment affected expression patterns in different at various stages of fish development. The observable affect seen in normal medaka fish was reversal of the male gonads and may affect bone formation (page 643). Further, preliminary results reported by Kawahara *et al.* for a transgenic medaka over-expressing the estrogen receptor is that transgenic fish is hyper-sensitive to estrogen and that estrogen treatment affects embryo development and in particular blood vessel development (page 648). Additionally, Kawahara *et al.* discuss the isolation of related estrogen receptors and indicates that the variants are expressed in both embryos and frys (page 648). Gray *et al.* (IDS reference) teach that estrogen treatment of medaka fish can affect a variety of phenotypes beyond sex determination including affecting the central nervous system (page 2587, second column). Clearly in medaka fish the affect of estrogen and the role of the various estrogen receptor variants is a complex system which still remains to be elucidated (Kawahara *et al.* page 648).

The art teaches that the *in vivo* expression of a transgene is dependent on the specific promoters used in the transgene construct, number of copies of the transgene inserted into the host genome, location in the genome and number of cells which contain the transgene can affect the phenotype of the resulting transgenic fish. While the methods for the introduction of a transgene are becoming routine in the art, the expression of the transgene and resulting phenotype of the animal is not predictable. Therefore, in view of the unexpected phenotype of a transgenic

medaka fish comprising within its genome a polynucleotide encoding a medaka estrogen receptor as set forth in SEQ ID NO: 2 operatively linked to the medaka beta-actin promoter, wherein said transgenic medaka fish produces increased level of the estrogen receptor as compared to normal wild type medaka fish and produce observable thrombi when cultured in the presence of estrogen, the present specification provides only the necessary guidance for said transgenic medaka fish and methods of use of said transgenic medaka fish in methods to detect estrogen in a sample and to develop transgenic medaka fish with thrombi. Absent correlative evidence or further guidance in light of the unpredictability of transgene behavior and the complexity of the estrogen receptor *in vivo*, the specification does not reasonably provide enablement for medaka fish which do not express the estrogen receptor, for other promoters besides the beta-actin promoter, or for the use of transgenic medaka fish which do not develop thrombi.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claims 8-13 are unclear in the in the recitation of 'raising the

transgenic medaka fish according to claim' because there is no method steps in the claims on which these claims depend, so it is unclear 'according' to what conditions the claims are referring. Claims 6 and 7 encompass a transgenic medaka fish, and amending claims to 8-11 to recite raising the transgenic medaka fish **of** claim' will obviate the basis of the rejection. Dependent claims 14-17 are included in the basis of the rejection because they fail to further clarify the basis of the rejection.

Claims 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claims 10 and 11 are recite and are drawn to 'Medaka fish having one or more thrombi' however the method by which they are obtained is by culturing transgenic medaka fish described in claims 6 and 7. The claims are confusing because it is not clear if the claim is drawn to any medaka fish having thrombi or transgenic medaka expressing the medaka estrogen receptor. If the claim is drawn only to a normal medaka, lacking any transgene, it is unclear how culturing a transgenic medaka will result in the loss of the transgene. More clearly indicating the type of fish, transgenic or normal, encompassed by the claim would obviate the basis of the rejection.

Claims 12 and 13 unclear in the recitation of 'estrogen-like action' because estrogen-like compounds do not demonstrate an action, rather the have inherent activities. Amending the claims to recite 'estrogen like activity' will obviate the basis of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 6-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Yamashita (EP 1 180 684 A1).

The instant application has not been benefit of the foreign application filing date because a translation has not been provided. As indicated above the priority date of the instant application is June 29, 2001. The filing date of EP 1 180 684 A1 is June 27, 2001 and had designated the United States as a contracting state, therefore EP 1 180 684 A1 qualifies as a 102(e) type reference.

DNA homology analysis indicates that the polynucleotide sequences taught by Yamashita are the same as taught in the instant specification. Further, the specification of Yashimita is essentially the same as the instant specification. In particular, Yashimita teaches that the polynucleotide sequence obtained from a medaka cDNA library encodes a estrogen receptor. Further, when the medaka estrogen receptor is expressed in transgenic medaka fish, the fish are

more sensitive to estrogen. When the transgenic medaka fish are cultured in the presence of estrogen, the fish develop observable thrombi. Finally, claims 5-10 of Yashimita are drawn to the same transgenic medaka fish comprising a medaka fish estrogen receptor and methods of use for developing thrombi and/or testing for the presence of estrogen in a sample by observing the formation of thrombi in transgenic medaka fish expressing the estrogen receptor. Since the sequences and the methods of use in generating transgenic Medaka fish disclosed by Yashimita are the same as instantly disclosed and claimed, the teachings of Yashimita anticipate the instant claims.

Claims 10 and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Kawahara *et al.* (IDS reference AU).

Claims 10 and 11 are a product by process drawn to a medaka fish which have been raised in the presence of estrogen. As noted above in the rejection made under 35 USC 112, second paragraph, the claim could reasonably be interpreted to encompass any medaka fish treated with estrogen. Kawahara *et al.* teach the characterization of an estrogen receptor in medaka fish. Further, Kawahara *et al.* report that preliminary results of transgenic medaka fish which over-express the receptor are hypersensitive to the affects of estrogen. Importantly, the transgenic medaka produced an observable alteration in the blood vessels (page 648, top of first column). It is noted that sequence homology comparisons indicates that the sequences disclosed by Kawahara *et al.* are not the same as disclosed in the instant specification, however because of

the breadth of the instant claims the transgenic medaka fish treated with estrogen and demonstrating an alteration in the blood vessels as taught by Kawahara *et al.* would anticipate the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

RAM R. SHUKLA, PH.D
PATENT EXAMINER